National Toxicology Program (NTP) Public Meeting on the Report on Carcinogens (RoC)

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National Library of Medicine, National Institutes of Health
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Comments by
Jennifer Sass, Ph.D.
Senior scientist, Health and Environment
Natural Resources Defense Council
1200 New York Avenue, NW, suite 400
Washington, DC 20005
email: jsass@nrdc.org

The criteria need an explicit description of how mechanistic data can be used to upgrade an agent

The NTP criteria for listing agent in the report on Carcinogens as "known to be human carcinogen" requires sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture, and human cancer."[1] The criteria also allows for conclusions on carcinogenicity to be based on "scientific judgment with consideration of all relevant information." This relevant information may include "mechanism of action" information. The criteria describe how mechanistic data may be used to delist/downgrade an agent that causes cancer in animals. The criteria state, "for example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonable be anticipated to cause cancer in humans." However, it is an obvious absence that the criteria lack an explicit description of how mechanistic data can be used to upgrade an agent, especially to "known human carcinogen." It is essential to have explicit criteria that allow the use of mechanistic data to list/upgrade an agent to 'known human carcinogen', where appropriate.

The NTP RoC needs to maximize the appropriate use of mechanistic data to properly inform the public of cancer hazards that they may encounter in the environment or workplace.

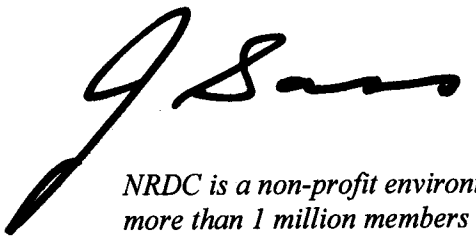
After presenting the criteria, the Report provides a definition of human studies; "traditional cancer epidemiology, data from clinical studies, and/or data derived from the study of tissues from humans exposed to the substance in questions and useful for evaluating whether a

[1] http://ntp-server.niehs.nih.gov/meetings/2004/AgendaRoC2004JanPM.pdf

relevant cancer mechanism is operating in people." This clarification should be part of the criteria. However, even this clarification is not sufficient. For example, vinyl chloride is a known human carcinogen, yet vinyl bromide and vinyl fluoride produce the same types of tumors in experimental animals (including the uncommon hemangeiosarcomas of the liver), the same types of DNA adducts in exposed animals, and the same metabolites by rodent and human liver microsomes as vinyl chloride. All of this information indicates that these vinyl halides act by a common mechanism and should be regarded as human carcinogens. It would be misleading for a worker to believe that his/her cancer risk is less when working with vinyl bromide[2] versus vinyl chloride, when it is possible that the reverse is true. The NTP RoC needs to maximize the appropriate use of mechanistic data to properly inform the public of cancer hazards that they may encounter in the environment or workplace.

Thank you for the opportunity to present comments,

Jennifer Sass



NRDC is a non-profit environmental action organization. We use law, science and the support of more than 1 million members and online activists to protect the planet's wildlife and wild places and to ensure a safe and healthy environment for all living things.

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[2] IARC. 1999. Vinyl bromide is *probably carcinogenic to humans (Group 2A)*."In making the overall evaluation, the Working Group took into consideration that all available studies showed a consistently parallel response between vinyl bromide and vinyl chloride. In addition, both vinyl chloride and vinyl bromide are activated via a P450-dependent pathway to their corresponding epoxides. For both vinyl chloride and vinyl bromide, the covalent binding of these compounds to DNA forms the respective etheno adducts. The weight of positive evidence for both compounds was also noted among the studies for genotoxicity, although the number and variety of tests for vinyl bromide were fewer." VOL.: 71 (1999) (p. 923)